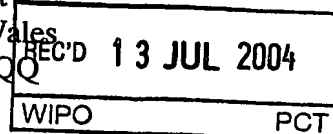




INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ



I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

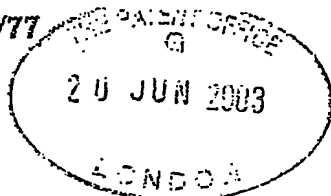
Signed

Andrew Gersey

Dated

1 July 2004

BEST AVAILABLE COPY



23JUN03 EB18819-2 C72481
P01/7700 0.00-0314490.4

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

PA 533

2. Patent application number

(The Patent Office will fill in this part)

0314490.4

20 JUN 2003

3. Full name, address and postcode of the or of each applicant (underline all surnames)

CELTECH R&D LIMITED
208 BATH ROAD

Patents ADP number (if you know it)

SLOUGH, SL1 3WE

If the applicant is a corporate body, give the country/state of its incorporation

BERKSHIRE
UK

8121485001

4. Title of the invention

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

CELTECH R&D LIMITED
PATENTS DEPARTMENT
208 BATH ROAD
SLOUGH, SL1 3WE
BERKSHIRE

Patents ADP number (if you know it)

8182305001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
Do not count copies of the same document

Continuation sheets of this form ☐ 0
Description ☒ 63
Claim(s) ☐ 0
Abstract ☐ 0
Drawing(s) ☐ 0

10. If you are also filing any of the following, state how many against each item.

Priority documents ☐ 0
Translations of priority documents ☐ 0
Statement of inventorship and right to grant of a patent (Patents Form 7/77) ☐ 0
Request for preliminary examination and search (Patents Form 9/77) ☐ 0
Request for substantive examination (Patents Form 10/77) ☐ 0
Any other documents (please specify) ☐ 0

11.

I/We request the grant of a patent on the basis of this application.
For and on Behalf of CELLTECH RES LTD.
Signature Date

[Signature] 20/6/03

12. Name and daytime telephone number of person to contact in the United Kingdom

DR. PHILLIP ANSELL 01753 534655

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered 'Yes' Patents Form 7/77 will need to be filed.
- Once you have filled in the form you must remember to sign and date it.
- For details of the fee and ways to pay please contact the Patent Office.

CHEMICAL COMPOUNDS

This invention relates to a series of thienopyridone derivatives, to
5 compositions containing them, to processes for their preparation and to their
use in medicine.

Immune and inflammatory responses involve a variety of cell types with
control and co-ordination of the various interactions occurring *via* both cell-
10 cell contacts (e.g. integrin interactions with their receptors) and by way of
intercellular signalling molecules. A large number of different signalling
molecules are involved, including cytokines, lymphocytes, chemokines and
growth factors.

15 Cells respond to such intercellular signalling molecules by means of
intracellular signalling mechanisms that include protein kinases,
phosphatases and phospholipases. There are five classes of protein kinase
of which the major ones are the tyrosine kinases and the serine/threonine
kinases [Hunter, T., Methods in Enzymology (Protein Kinase Classification)
20 p. 3, Hunter, T. and Sefton, B.M.; eds. Vol. 200, Academic Press; San Diego,
1991].

One sub-class of serine/threonine kinases is the mitogen activating protein
(MAP) kinases of which there are at least three families which differ in the
25 sequence and size of the activation loop [Adams, J. L. *et al*, Progress in
Medicinal Chemistry p. 1-60, King, F. D. and Oxford, A. W.; eds. vol 38,
Elsevier Science, 2001]: (i) the extracellular regulated kinases (ERKs), (ii) the
c-Jun NH₂ terminal kinases or stress activated kinases (JNKs or SAP
kinases) and (iii) the p38 kinases which have a threonine-glycine-tyrosine
30 (TGY) activation motif. Both the JNKs and p38 MAP kinases are primarily
activated by stress stimuli including, but not limited to, proinflammatory
cytokines e.g. tumour necrosis factor (TNF) and interleukin-1 (IL-1),
ultraviolet light, endotoxin and chemical or osmotic shock.

Four isoforms of p38 have been described (p38 α / β / γ / δ). The human p38 α enzyme was initially identified as a target of cytokine-suppressive anti-inflammatory drugs (CSAIDs) and the two isoenzymes found were initially
5 termed CSAID binding protein-1 (CSBP-1) and CSBP-2 [Lee, J. C. *et al*, Nature (London) 1994, 372, 739-46]. CSBP-2 is now widely referred to as p38 α and differs from CSBP-1 in an internal sequence of 25 amino acids as a result of differential splicing of two exons that are conserved in both mouse and human [McDonnell, P. C. *et al*, Genomics 1995, 29, 301-2]. CSBP-1 and
10 p38 α are expressed ubiquitously and there is no difference between the two isoforms with respect to tissue distribution, activation profile, substrate preference or CSAID binding. A second isoform is p38 β which has 70% identity with p38 α . A second form of p38 β termed p38 β 2 is also known and of the two this is believed to be the major form. p38 α and p38 β 2 are expressed
15 in many different tissues. However in monocytes and macrophages p38 α is the predominant kinase activity [Lee, J. C., *ibid*; Jing, Y. *et al*, J. Biol. Chem. 1996, 271, 10531-34; Hale, K. K. *et al*, J. Immun. 1999, 162, 4246-52]. p38 γ and p38 δ (also termed SAP kinase-3 and SAP kinase-4 respectively) have ~63% and ~61% homology to p38 α respectively. p38 γ is predominantly
20 expressed in skeletal muscle whilst p38 δ is found in testes, pancreas, prostate, small intestine and in certain endocrine tissues.

All p38 homologues and splice variants contain a 12 amino acid activation loop that includes a Thr-Gly-Tyr motif. Dual phosphorylation of both Thr-180
25 and Tyr-182 in the TGY motif by a dual specificity upstream kinase is essential for the activation of p38 and results in a >1000-fold increase in specific activity of these enzymes [Doza, Y. N. *et al* FEBS Lett., 1995, 364, 7095-8012]. This dual phosphorylation is effected by MKK6 and under certain conditions the related enzyme MKK3 [Enslin, H. *et al* J. Biol. Chem., 1998,
30 273, 1741-48]. MKK3 and MKK6 belong to a family of enzymes termed

MAPKK (mitogen activating protein kinase kinase) which are in turn activated by MAPKKK (mitogen activating kinase kinase kinase) otherwise known as MAP3K.

- 5 Several MAP3Ks have been identified that are activated by a wide variety of stimuli including environmental stress, inflammatory cytokines and other factors. MEKK4/MTK1 (MAP or ERK kinase kinase/MAP three kinase-1), ASK1 (apoptosis stimulated kinase) and TAK1 (TGF- β -activated kinase) are some of the enzymes identified as upstream activators of for MAPKKs.
- 10 MEKK4/MTK1 is thought to be activated by several GADD-45-like genes that are induced in response to environmental stimuli and which eventually lead to p38 activation [Takekawa, M. and Saito, H. Cell, 1998, 95, 521-30]. TAK1 has been shown to activate MKK6 in response to transforming growth factor- β (TGF- β). TNF-stimulated activation of p38 is believed to be mediated by the
- 15 recruitment of TRAF2 [TNF receptor associated factor] and the Fas adaptor protein, Daxx, which results in the activation of ASK1 and subsequently p38.

Several substrates of p38 have been identified including other kinases [e.g. MAPK activated protein kinase 2/3/5 (MAPKAP 2/3/5), p38

20 regulated/activated protein kinase (PRAK), MAP kinase-interacting kinase 1/2 (MNK1/2), mitogen- and stress-activated protein kinase 1 (MSK1/RLPK) and ribosomal S6 kinase-B (RSK-B)]; transcription factors [e.g. activating transcription factor 2/6 (ATF2/6), monocyte-enhancer factor-2A/C (MEF2A/C), C/EBP homologous protein (CHOP), Elk1 and Sap-1a1]; and

25 other substrates [e.g. cPLA2, p47phox].

MAPKAP K2 is activated by p38 in response to environmental stress. Mice engineered to lack MAPKAP K2 do not produce TNF in response to lipopolysaccharide (LPS). Production of several other cytokines such as IL-1,

30 IL-6, IFN-g and IL-10 is also partially inhibited [Kotlyarov, A. *et al* Nature Cell Biol. 1999, 1, 94-7]. Further, MAPKAP K2 from embryonic stem cells from

p38 α null mice was not activated in response to stress and these cells did not produce IL-6 in response to IL-1 [Allen, M. *et al*, J. Exp. Med. 2000, 191, 859-69]. These results indicate that MAPKAP K2 is not only essential for TNF and IL-1 production but also for signalling induced by cytokines. In addition
5 MAPKAP K2/3 phosphorylate and thus regulate heat shock proteins HSP 25 and HSP 27 which are involved in cytoskeletal reorganization.

Several small molecule inhibitors of p38 have been reported which inhibit IL-1 and TNF synthesis in human monocytes at concentrations in the low μ M
10 range [Lee, J. C. *et al*, Int. J. Immunopharm. 1988, 10, 835] and exhibit activity in animal models which are refractory to cyclooxygenase inhibitors [Lee, J. C. *et al*, Annals N. Y. Acad. Sci. 1993, 696, 149]. In addition these small molecule inhibitors are known to decrease the synthesis of a wide variety of pro-inflammatory proteins including IL-6, IL-8,
15 granulocyte/macrophage colony-stimulating factor (GM-CSF) and cyclooxygenase-2 (COX-2). TNF-induced phosphorylation and activation of cytosolic PLA₂, TNF-induced expression of VCAM-1 on endothelial cells and IL-1 stimulated synthesis of collagenase and stromelysin are also inhibited by small molecule inhibitors of p38 [Cohen, P. Trends Cell Biol. 1997, 7, 353-
20 61].

A variety of cells including monocytes and macrophages produce TNF and IL-1. Excessive or unregulated TNF production is implicated in a number of disease states including Crohn's disease, ulcerative colitis, pyresis,
25 rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, toxic shock syndrome, endotoxic shock, sepsis, septic shock, gram negative sepsis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary
30 sarcoisosis, cerebral malaria, scar tissue formation, keloid formation, fever and myalgias due to infection, such as influenza, cachexia secondary to

acquired immune deficiency syndrome (AIDS), cachexia secondary to infection or malignancy, AIDS or AIDS related complex.

Excessive or unregulated IL-1 production has been implicated in rheumatoid arthritis, osteoarthritis, traumatic arthritis, rubella arthritis, acute synovitis, psoriatic arthritis, cachexia, Reiter's syndrome, endotoxemia, toxic shock syndrome, tuberculosis, atherosclerosis, muscle degeneration, and other acute or chronic inflammatory diseases such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease. In addition IL-1 has been linked to diabetes and pancreatic β cells [Dinarello, C. A. J. Clinical Immunology, 1985, 5, 287-97].

IL-8 is a chemotactic factor produced by various cell types including endothelial cells, mononuclear cells, fibroblasts and keratinocytes. IL-1, TNF and LPS all induce the production of IL-8 by endothelial cells. *In vitro* IL-8 has been shown to have a number of functions including being a chemoattractant for neutrophils, T-lymphocytes and basophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without *de novo* protein synthesis which may contribute to increased adhesion of neutrophils to vascular endothelial cells. Many diseases are characterised by massive neutrophil infiltration. Histamine release from basophils (in both atopic and normal individuals) is induced by IL-8 as is lysozomal enzyme release and respiratory burst from neutrophils.

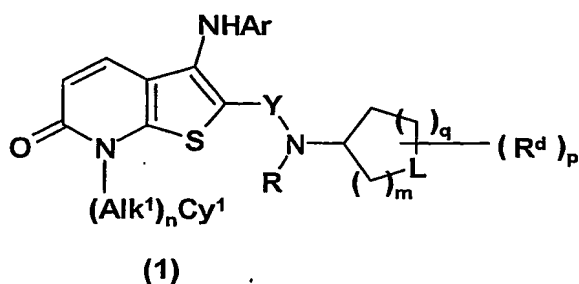
The central role of IL-1 and TNF together with other leukocyte derived cytokines as important and critical inflammatory mediators is well documented. The inhibition of these cytokines has been shown or would be expected to be of benefit in controlling, alleviating or reducing many of these disease states.

30

The central position that p38 occupies within the cascade of signalling molecules mediating extracellular to intracellular signalling and its influence over not only IL-1, TNF and IL-8 production but also the synthesis and/or action of other pro-inflammatory proteins (e.g. IL-6, GM-CSF, COX-2, collagenase and stromelysin) make it an attractive target for inhibition by small molecule inhibitors with the expectation that such inhibition would be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. Such an expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors [Adams, *ibid*; Badger, *et al*, J. Pharm. Exp. Ther. 1996, 279, 1453-61; Griswold, *et al*, Pharmacol. Comm., 1996, 7, 323-29].

We have now found a group of compounds which are potent and selective inhibitors of p38 kinase (p38 α , β , δ and γ) and the isoforms and splice variants thereof, especially p38 α , p38 β and p38 β 2. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described herein.

Thus according to one aspect of the invention we provide a compound of formula (1) :



wherein:

Y is a linking group $-C(O)-$ or $-S(O_2)-$;

n is zero or the integer 1;

m is the integer 1, 2 or 3;

p is the integer 1, 2, 3 or 4;

5 q is zero or the integer 1 or 2;

R is a hydrogen atom or a straight or branched C_{1-6} alkyl group;

R^d is an $-OH$, $-(Alk^2)OH$ (where Alk^2 is a straight or branched C_{1-4} alkylene chain), $-OR^1$ (where R^1 is a straight or branched C_{1-6} alkyl group), $-(Alk^2)OR^1$, $-NR^2R^3$ (where R^2 and R^3 may be the same or different and is each

10 independently a hydrogen atom or straight or branched C_{1-6} alkyl group), $-(Alk^2)NR^2R^3$ or straight or branched C_{1-6} alkyl group;

L is a linking atom or group $-O-$, $-S-$, $-S(O)-$, $-S(O_2)-$, $-CH_2-$, $-CH(R^d)-$, $-C(R^d)_2-$ or $-NR^y-$ where R^y is a hydrogen atom or a C_{1-4} alkyl group;

Cy^1 is a substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic,

15 polyheterocycloaliphatic, aromatic or heteroaromatic group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

It will be appreciated that compounds of formula (1) may have one or more

20 chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist

25 as tautomers, for example keto ($CH_2C=O$)-enol ($CH=CHOH$) tautomers.

Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

The following general terms as used herein in relation to compounds of the invention and intermediates thereto have the stated meaning below unless specifically defined otherwise.

- 5 Thus as used herein the term "alkyl" whether present as a group or part of a group includes straight or branched C₁₋₆alkyl groups, for example C₁₋₄alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl or t-butyl groups. Similarly, the terms "alkenyl" or "alkynyl" are intended to mean straight or branched C₂₋₆alkenyl or C₂₋₆alkynyl groups such as C₂₋₄alkenyl or
- 10 C₂₋₄alkynyl groups. The optional substituents which may be present on these groups include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, -CO₂H, -CO₂R⁴ [where R⁴ is an optionally substituted straight or branched C₁₋₆alkyl group, and is in particular a
- 15 straight or branched C₁₋₄alkyl group], e.g. -CO₂CH₃ or -CO₂C(CH₃)₃, -CONHR⁴, e.g. -CONHCH₃, -CON(R⁴)₂, e.g. -CON(CH₃)₂, -COR⁴, e.g. -COCH₃, C₁₋₆alkoxy, e.g. methoxy or ethoxy, haloC₁₋₆alkoxy, e.g. trifluoromethoxy or difluoromethoxy, thiol (-SH), -S(O)R⁴, e.g. -S(O)CH₃, -S(O)₂R⁴, e.g. -S(O)₂CH₃, C₁₋₆alkylthio e.g. methylthio or ethylthio, amino, -
- 20 NHR⁴, e.g. -NHCH₃ or -N(R⁴)₂, e.g. -N(CH₃)₂ groups. Where two R⁴ groups are present in any of the above substituents these may be the same or different.

- In addition when two R⁴ alkyl groups are present in any of the optional
- 25 substituents just described these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from -O-, -S-, -N(R⁴)-, -C(O)- or -C(S)- groups. Particular examples of such heterocyclic rings include
- 30 piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

The term halogen is intended to include fluorine, chlorine, bromine or iodine atoms.

- 5 The term "haloalkyl" is intended to include those alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CHF}_2$, $-\text{CHCl}_2$, $-\text{CH}_2\text{F}$ and $-\text{CH}_2\text{Cl}$ groups.
- 10 The term "alkoxy" as used herein is intended to include straight or branched C_{1-6} alkoxy e.g. C_{1-4} alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, i-butoxy and t-butoxy. "Haloalkoxy" as used herein includes any of these alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCH}_2\text{F}$ and $-\text{OCH}_2\text{Cl}$ groups.
- 15

As used herein the term "alkylthio" is intended to include straight or branched C_{1-6} alkylthio, e.g. C_{1-4} alkylthio such as methylthio or ethylthio.

- 20 As used herein the term "alkylamino or dialkylamino" is intended to include the groups $-\text{NHR}^{1a}$ and $-\text{N}(\text{R}^{1a})(\text{R}^{1b})$ where R^{1a} and R^{1b} is each independently an optionally substituted straight or branched alkyl group or both together with the N atom to which they are attached form an optionally substituted heterocycloalkyl group which may contain a further heteroatom or
- 25 heteroatom containing group such as an $-\text{O}-$ or $-\text{S}-$ atom or $-\text{N}(\text{R}^{1a})-$ group. Particular examples of such optionally substituted heterocycloalkyl groups include optionally substituted pyrrolidiny, piperidiny, morpholinyl, thiomorpholinyl and $\text{N}'\text{-C}_{1-6}$ alkyl-piperazinyl groups. The optional substituents which may be present on such heterocycloalkyl groups include those optional
- 30 substituents as described above in relation to the term "alkyl".

Particular examples of alkylene chains represented by Alk^1 and/or Alk^2 when each is present in compounds of the invention include $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2-$, $-(\text{CH}_2)_3\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$ chains.

5

Optionally substituted cycloaliphatic groups represented by the group Cy^1 in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g. C_{3-7} cycloalkenyl groups.

10

Particular examples of cycloaliphatic groups represented by the group Cy^1 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, or 3-cyclopenten-1-yl groups.

15

The optional substituents which may be present on the cycloaliphatic groups represented by the group Cy^1 include one, two, three or more substituents selected from halogen atoms, or C_{1-6} alkyl, e.g. methyl or ethyl, halo C_{1-6} alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-\text{C}(\text{OH})(\text{CF}_3)_2$, C_{1-6} alkoxy, e.g. methoxy or ethoxy, halo C_{1-6} alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6} alkylthiol, e.g. methylthiol or ethylthiol, carbonyl ($=\text{O}$), thiocarbonyl ($=\text{S}$), imino ($=\text{NR}^{4a}$) [where R^{4a} is an $-\text{OH}$ group or a C_{1-6} alkyl group], or $-(\text{Alk}^3)_v\text{R}^5$ groups in which Alk^3 is a straight

20

or branched C_{1-3} alkylene chain, v is zero or the integer 1 and R^5 is a C_{3-8} cycloalkyl, $-\text{OH}$, $-\text{SH}$, $-\text{N}(\text{R}^6)(\text{R}^7)$ [in which R^6 and R^7 is each independently selected from a hydrogen atom or an optionally substituted alkyl or C_{3-8} cycloalkyl group], $-\text{OR}^6$, $-\text{SR}^6$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^6$, $-\text{SOR}^6$, $-\text{SO}_2\text{R}^6$, $-\text{SO}_3\text{R}^6$, $-\text{OCO}_2\text{R}^6$, $-\text{C}(\text{O})\text{R}^6$, $-\text{OC}(\text{O})\text{R}^6$, $-\text{C}(\text{S})\text{R}^6$, $-\text{C}(\text{O})\text{N}(\text{R}^6)(\text{R}^7)$, $-\text{OC}(\text{O})\text{N}(\text{R}^6)(\text{R}^7)$, $-\text{N}(\text{R}^6)\text{C}(\text{O})\text{R}^7$, $-\text{C}(\text{S})\text{N}(\text{R}^6)(\text{R}^7)$, $-\text{N}(\text{R}^6)\text{C}(\text{S})\text{R}^7$, $-\text{SO}_2\text{N}(\text{R}^6)(\text{R}^7)$, $-\text{N}(\text{R}^6)\text{SO}_2\text{R}^7$, $-\text{N}(\text{R}^6)\text{C}(\text{O})\text{N}(\text{R}^7)(\text{R}^8)$ [where R^8 is as defined for R^6], $-\text{N}(\text{R}^6)\text{C}(\text{S})\text{N}(\text{R}^7)(\text{R}^8)$, $-\text{N}(\text{R}^6)\text{C}(\text{O})\text{N}(\text{R}^7)(\text{R}^8)$]

30

N(R⁶)SO₂N(R⁷)(R⁸) or an optionally substituted aromatic or heteroaromatic group.

Particular examples of Alk³ chains include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-
5 and -CH(CH₃)CH₂- chains.

When R⁵, R⁶, R⁷ and/or R⁸ is present as a C₃₋₈cycloalkyl group it may be for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Optional substituents which may be present on such groups include for example one,
10 two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C₁₋₆alkoxy, e.g. methoxy, ethoxy or *i*-propoxy groups.

When the groups R⁶ and R⁷ or R⁷ and R⁸ are both alkyl groups these groups
15 may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from -O-, -S-, -N(R⁷)-, -C(O)- or -C(S)- groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl,
20 pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When R⁵ is an optionally substituted aromatic or heteroaromatic group it may be any such group as described hereinafter in relation to Cy¹.

25

In general, optionally substituted aromatic groups represented by the group Cy¹ include for example monocyclic or bicyclic fused ring C₆₋₁₂aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or
30 indenyl groups.

Heteroaromatic groups represented by the group Cy¹ include for example C₁₋₉ heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, [2,3-dihydro]benzothienyl, benzotriazolyl, indolyl, indolinyl, indazolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-a]pyrazinyl, imidazo[1,5-c]pyrimidinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, phthalazinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, imidyl, e.g. succinimidyl, phthalimidyl or naphthalimidyl such as 1,8-naphthalimidyl, pyrazolo[4,3-d]pyrimidinyl, furo[3,2-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, pyrrolo[3,2-d]pyrimidinyl, pyrazolo[3,2-b]pyridinyl, furo[3,2-b]pyridinyl, thieno[3,2-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, thiazolo[3,2-a]pyridinyl, pyrido[1,2-a]pyrimidinyl, tetrahydroimidazo[1,2-a]pyrimidinyl and dihydroimidazo[1,2-a]pyrimidinyl groups.

Optional substituents which may be present on aromatic or heteroaromatic groups represented by the group Cy^1 include one, two, three or more substituents, each selected from an atom or group R^{10} in which R^{10} is R^{10a} or $-L^6Alk^5(R^{10a})_r$, where R^{10a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl ($-OH$), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), substituted thiol, $-COR^{11}$ [where R^{11} is an $-L^6Alk^3(R^{10a})_r$, aryl or heteroaryl group], $-CSR^{11}$, $-SO_3H$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-SO_2NH_2$, $-SO_2NHR^{11}$, $-SO_2N(R^{11})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{11}$, $-CSNHR^{11}$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-N(R^{12})SO_2R^{11}$ [where R^{12} is a hydrogen atom or a straight or branched alkyl group], $-N(SO_2R^{11})_2$, $-N(R^{12})SO_2NH_2$, $-N(R^{12})SO_2NHR^{11}$, $-N(R^{12})SO_2N(R^{11})_2$, $-N(R^{12})COR^{11}$, $-N(R^{12})CONH_2$, $-N(R^{12})CONHR^{11}$, $-N(R^{12})CON(R^{11})_2$, $-N(R^{12})CSNH_2$, $-N(R^{12})CSNHR^{11}$, $-N(R^{12})CSN(R^{11})_2$, $-N(R^{12})CSR^{11}$, $-N(R^{12})C(O)OR^{11}$, $-C=NR^{12}(NR^{12})$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{3-7} cyclicamino group optionally containing one or more other $-O-$ or $-S-$ atoms or $-N(R^{12})-$, $-C(O)-$ or $-C(S)-$ groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{12})SO_2NHet^1$, $-N(R^{12})CONHet^1$, $-N(R^{12})CSNHet^1$, $-SO_2N(R^{12})Het$ [where $-Het$ is an optionally substituted monocyclic C_{3-7} carbocyclic group optionally containing one or more other $-O-$ or $-S-$ atoms or $-N(R^{12})-$, $-C(O)-$, $-S(O)-$ or $-S(O)_2-$ groups], $-Het$, $-CON(R^{12})Het$, $-CSN(R^{12})Het$, $-N(R^{12})CON(R^{12})Het$, $-N(R^{12})CSN(R^{12})Het$, $-N(R^{12})SO_2N(R^{12})Het$, aryl or heteroaryl groups; L^6 is a covalent bond or a linker atom or group; Alk^5 is an optionally substituted straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three $-O-$ or $-S-$ atoms or $-S(O)_n-$ [where n is an integer 1 or 2] or $-N(R^{12})-$ e.g. $-N(CH_3)-$ groups; and r is zero or the integer 1, 2, or 3. It will be appreciated that when two R^{11} or R^{12} groups are present in one of the above substituents the R^{11} and R^{12} groups may be the same or different.

When L^6 in the group $-L^6Alk^5(R^{10a})_r$ is a linker atom or group it may be for example any divalent linking atom or group. Particular examples include $-O-$ or $-S-$ atoms or $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, $-N(R^3)-$

[where R^3 is a hydrogen atom or a straight or branched alkyl group], $-N(R^3)O-$, $-N(R^3)N-$, $-CON(R^3)-$, $-OC(O)N(R^3)-$, $-CSN(R^3)-$, $-N(R^3)CO-$, $-N(R^3)C(O)O-$, $-N(R^3)CS-$, $-S(O)_2N(R^3)-$, $-N(R^3)S(O)_2-$, $-N(R^3)CON(R^3)-$, $-N(R^3)CSN(R^3)-$ or $-N(R^3)SO_2N(R^3)-$ groups. Where L^6 contains two R^3 groups these may be the same or different.

When in the group $-L^6Alk^5(R^{10a})_r$, r is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{10a} may be present on any suitable carbon atom in $-Alk^5$. Where more than one R^{10a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^5$. Clearly, when r is zero and no substituent R^{10a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^5 becomes an alkyl, alkenyl or alkynyl group.

When R^{10a} is a substituted amino group it may be for example a group $-NHR^{11}$ [where R^{11} is as defined above] or a group $-N(R^{11})_2$ wherein each R^{11} group is the same or different.

When R^{10a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{10a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{11}$ or a $-SR^{12}$ group respectively.

Esterified carboxyl groups represented by the group R^{10a} include groups of formula $-CO_2Alk^6$ wherein Alk^6 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted

phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C₆₋₁₂aroyloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk⁶ group include R^{10a} atoms and groups as described above.

When Alk⁵ is present in or as a substituent it may be for example a -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH(CH₃)CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH(CH₃)CH₂CH₂-, -C(CH₃)₂CH₂-, -CH=CH-, -CH=CCH₂-, -CH₂C=CH-, -CH=CHCH₂CH₂-, -CH₂CH=CHCH₂-, -CH₂CH₂CH=CH₂-, -CC-, -CCCH₂-, -CH₂CC-, -CCCH₂CH₂-, -CH₂CCCH₂- or -CH₂CH₂CC- chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R¹²)-, e.g. -N(CH₃)- groups. The aliphatic chains represented by Alk⁵ may be optionally substituted by one, two or three halogen atoms in addition to any R^{10a} groups that may be present.

Aryl or heteroaryl groups represented by the groups R^{10a} or R¹¹ include mono- or bicyclic optionally substituted C₆₋₁₂ aromatic or C₁₋₉ heteroaromatic groups as described above for the group Cy¹. The aromatic and heteroaromatic groups may be attached to the group Cy¹ in compounds of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

It will be appreciated that when -NHet¹ or -Het forms part of a substituent R¹⁰ the heteroatoms or heteroatom containing groups that may be present within the ring -NHet¹ or -Het take the place of carbon atoms within the parent carbocyclic ring.

Thus when -NHet¹ or -Het forms part of a substituent R¹⁰ each may be for example an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group.

Additionally Het may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ include those substituents described above when Cy¹ is a heterocycloaliphatic group.

5

Particularly useful atoms or groups represented by R¹⁰ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, or thienyl, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₃₋₇cycloalkyl, e.g. cyclobutyl, cyclopentyl, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino, ethylamino, -CH(CH₃)NH₂ or -C(CH₃)₂NH₂, haloC₁₋₆alkylamino, e.g. fluoroC₁₋₆alkylamino, e.g. -CH(CF₃)NH₂ or -C(CF₃)₂NH₂, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁶ [where Alk⁶ is as defined above], C₁₋₆alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g.

methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylamino-carbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethyl-aminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylamino-carbonylamino, e.g. dimethylaminocarbonylamino or diethylamino-carbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylamino-carbonylmethylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocabonyl-amino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonylamino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino, e.g. ethylaminothiocabonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridylmethylthio or thiazolylmethylthio groups.

30

A further particularly useful group of substituents represented by R^{10} when present on aromatic or heteroaromatic groups includes substituents of formula $-L^6Alk^5R^{10a}$ where L^6 is preferably a covalent bond or an $-O-$ or $-S-$ atom or $-N(R^3)-$, $-C(O)-$, $-C(O)O-$, $-O-C(O)-$, $-N(R^3)CO-$, $-CON(R^3)-$ or $-N(R^3)S(O)_2-$ group, Alk^5 is an optionally substituted C_{1-6} alkyl group optionally interrupted by one or two $-O-$ or $-S-$ atoms or $-N(R^{12})-$, $-C(O)-$, $-C(S)-$, $-CON(R^{12})-$ or $-N(R^{12})CO-$ groups and R^{10a} is an optionally substituted Het group as herein defined or an optionally substituted heteroaromatic group as hereinbefore described in relation to Cy^1 .

10

Where desired, two R^{10} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6} alkylenedioxy group such as methylenedioxy or ethylenedioxy.

15 It will be appreciated that where two or more R^{10} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position on the aromatic or heteroaromatic group represented by the group Cy^1 .

20 The substituted aromatic or heteroaromatic group represented by Ar in compounds of the invention may be any aromatic or heteroaromatic group as hereinbefore described for Cy^1 . Optional substituents which may be present include those R^{10} atoms and groups as generally or particularly described in relation to Cy^1 aromatic and heteroaromatic groups.

25

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic

30 bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulfonates, e.g. methanesulfonates, ethanesulfonates, or isothionates, arylsulfonates, e.g. *p*-toluenesulfonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

When in compounds of formula (1) n is the integer 1, Alk^1 is preferably a $-\text{CH}_2\text{CH}_2-$ chain or more especially is $-\text{CH}_2-$.

In one class of compounds of formula (1) n is zero.

Particularly preferred Cy^1 optionally substituted cycloaliphatic groups include optionally substituted C_{3-7} cycloalkyl groups, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups. Cy^1 is in particular a cyclopropyl group.

Each of these preferred Cy^1 cycloalkyl groups may be unsubstituted. When substituents are present these may in particular include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6} alkyl groups, especially C_{1-3} alkyl groups, most especially a methyl group, or a halo C_{1-6} alkyl group, especially a fluoro C_{1-6} alkyl group, most especially a $-\text{CF}_3$ group, or a C_1 -

alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a haloC₁₋₆alkoxy, especially a fluoroC₁₋₆alkoxy, most especially a -OCF₃ group, or a cyano (-CN), esterified carboxyl, especially -CO₂CH₃ or -CO₂C(CH₃)₃, nitro (-NO₂), amino (-NH₂), substituted amino, especially -NHCH₃ or -N(CH₃)₂, -
5 C(O)R⁶, especially -C(O)CH₃, or -N(R⁶)C(O)R⁷, especially -NHCOCH₃ group.

Particularly preferred Cy¹ aromatic groups include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include
10 optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl,
15 oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group. In a further preference, the heteroaromatic group may be an eight- to thirteen-membered bicyclic fused ring containing one or two oxygen, sulphur or nitrogen atoms. Particularly useful groups of this type include optionally substituted indolyl groups.

20 Particularly preferred optional substituents which may be present on Cy¹ aromatic or heteroaromatic groups include one, two or three atoms or groups -R^{10a} or -L⁶Alk⁵(R^{10a})_r as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine
25 atoms, or C₁₋₆alkyl groups, especially C₁₋₃alkyl groups, most especially a methyl group, or a haloC₁₋₆alkyl group, especially a fluoroC₁₋₆alkyl group, most especially a -CF₃ group, or a C₁₋₆alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a haloC₁₋₆alkoxy, especially a fluoroC₁₋₆alkoxy, most especially a -OCF₃ group, or a cyano (-CN), carboxyl (-CO₂H),
30 esterified carboxyl (-CO₂Alk⁶), especially -CO₂CH₃, -CO₂CH₂CH₃, or -CO₂C(CH₃)₃, nitro (-NO₂), amino (-NH₂), substituted amino, especially -

NHCH₃ or -N(CH₃)₂, -COR¹¹, especially -COCH₃, or -N(R¹²)COR¹¹, especially -NHCOCH₃ group.

Further preferred optional substituents which may be present on Cy¹ aromatic or heteroaromatic groups include groups of formula -L⁶Alk⁵(R^{10a})_r, in which r is the integer 1 or 2, L⁶ is a covalent bond or an -O- or -S- atom or a -N(R³)-, especially -NH- or -N(CH₃)-, -C(O)-, -C(S)-, -C(O)O-, -OC(O)-, -N(R³)CO-, especially -NHCO-, or -CON(R³)-, especially -CHNH-group, Alk⁵ is a C₁₋₆alkyl chain, especially a -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- or -CH₂CH₂CH₂CH₂- chain and R^{10a} is a hydroxyl or substituted hydroxyl group, especially a -OCH₃, -OCH₂CH₃ or -OCH(CH₃)₂ group or a -NH₂ or substituted amino group, especially a -N(CH₃)₂ or -N(CH₂CH₃)₂ group or a -Het group, especially an optionally substituted monocyclic C₅₋₇carbocyclic group containing one, two or three -O-, -S-, -N(R¹²)-, especially -NH- or -N(CH₃)- or -C(O)- groups within the ring structure as previously described, most especially an optionally substituted pyrrolidinyl, imidazolidinyl, piperidinyl, e.g. N-methylpiperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group or R^{10a} is an optionally substituted heteroaromatic group, especially a five- or six-membered monocyclic heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms, such as optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl, triazinyl, pyridazinyl, or pyrazinyl group. Particularly preferred optional substituents on the -Het groups just described include hydroxyl (-OH) and carboxyl (-CO₂H) groups or those preferred optional substituents just described in relation to the group Cy¹, especially when Cy¹ is a cycloalkyl group.

In one particularly preferred group of compounds of formula (1) Cy¹ is an optionally substituted phenyl group, especially a phenyl group optionally substituted by one, two or three substituents where at least one, and preferably two substituents are located *ortho* to the bond joining Cy¹ to the

- remainder of the compound of formula (1). Particularly preferred *ortho* substituents include halogen atoms, especially fluorine or chlorine atoms, or C₁₋₃alkyl groups, especially methyl groups, C₁₋₃alkoxy groups, especially methoxy, haloC₁₋₃alkyl groups, especially -CF₃, haloC₁₋₃alkoxy groups, especially -OCF₃, or cyano (-CN), groups. In this class of compounds a second or third optional substituent when present in a position other than the *ortho* positions of the ring Cy¹ may be preferably an atom or group -R^{10a} or -L⁶Alk⁵(R^{10a})_r, as herein generally and particularly described. In another preference, the Cy¹ phenyl group may have a substituent *para* to the bond joining Cy¹ to the remainder of the compound of formula (1). Particular *para* substituents include those particularly preferred *ortho* substituents just described. Where desired, the *para* substituent may be present with other *ortho* or *meta* substituents as just mentioned.
- 15 Particularly preferred Ar aromatic groups in compounds of formula (1) include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

- Particularly preferred optional substituents which may be present on Ar aromatic or heteroaromatic groups include atoms or groups -R^{10a} or -L⁶Alk⁵(R^{10a})_r, as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C₁₋₆alkyl groups, especially C₁₋₃alkyl groups, most especially a methyl group, or a haloC₁₋₆alkyl group, especially a fluoroC₁₋₆alkyl group, most especially a -CF₃ group, or a C₁₋₆alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a haloC₁₋₆alkoxy, especially a fluoroC₁₋₆alkoxy, most especially a -

OCF₃ group, or a cyano (-CN), esterified carboxyl, especially -CO₂CH₃ or -CO₂C(CH₃)₃, nitro (-NO₂), amino (-NH₂), substituted amino, especially -NHCH₃ or -N(CH₃)₂, -COR¹¹, especially -COCH₃, or -N(R¹²)COR¹¹, especially -NHCOCH₃ group.

5

Particularly useful Ar groups in compounds of formula (1) include phenyl and mono- or disubstituted phenyl groups in which each substituent is in particular a -R^{10a} or -L⁶Alk⁵(R^{10a})_r atom or group as just defined and is especially a halogen atom or a C₁₋₃alkyl, C₁₋₃alkoxy or -CN group

10

Particular examples of Alk² when present in compounds of the invention include -CH₂-, -CH₂CH₂-, -C(CH₃)₂- and -CH(CH₃)CH₂-.

The group R in compounds of formula (1) is preferably a hydrogen atom.

15

L in compounds of the invention is in particular a -CH₂-, -CH(R^d)-, -NH- or -N(CH₃)- group.

In compounds of the invention, m and q may be selected to vary the ring size from a ring having any number of total ring members from 4 up to 8 inclusive. Particularly advantageous rings are those wherein m and q are selected to provide rings having a total of 4, 5 or 6 members

20

Each substituent R^d may be present on any ring carbon atom. In one particular class of compounds of the invention one or two R^d substituents are present.

25

Particular R^d substituents include -OH, -CH₂OH, -CH(CH₃)OH and -C(CH₃)₂OH groups.

30

Particularly useful compounds of the invention include each of the compounds described in the Examples hereinafter, and the salts, solvates, hydrates and N-oxides thereof.

- 5 Compounds according to the invention are potent and selective inhibitors of p38 kinases, including all isoforms and splice variants thereof. More specifically the compounds of the invention are inhibitors of p38 α , p38 β and p38 β 2. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples
10 hereinafter.

The compounds of formula (1) are of use in modulating the activity of p38 kinases and in particular are of use in the prophylaxis and treatment of any p38 kinase mediated diseases or disorders in a human, or other mammal.

- 15 The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders. Further the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating any such disease or disorder.

- 20 The invention also extends to the prophylaxis or treatment of any disease or disorder in which p38 kinase plays a role including conditions caused by excessive or unregulated pro-inflammatory cytokine production including for example excessive or unregulated TNF, IL-1, IL-6 and IL-8 production in a human, or other mammal. The invention extends to such a use and to the
25 use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Further the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating any such disease or disorder.

- 30 Diseases or disorders in which p38 kinase plays a role either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8

include without limitation autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

Autoimmune diseases which may be prevented or treated include but are not limited to rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs, host disease or psoriasis.

The invention further extends to the particular autoimmune disease rheumatoid arthritis.

Inflammatory diseases which may be prevented or treated include but are not limited to asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis.

Destructive bone disorders which may be prevented or treated include but are not limited to osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Proliferative diseases which may be prevented or treated include but are not limited to acute or chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma and multiple myeloma.

Neurodegenerative diseases which may be prevented or treated include but are not limited to Parkinson's disease, Alzheimer's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury.

- 5 Viral diseases which may be prevented or treated include but are not limited to acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

- 10 Infectious diseases which may be prevented or treated include but are not limited to septic shock, sepsis and Shigellosis.

In addition, p38 inhibitors of this invention also exhibit inhibition of expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxidase synthetase-2, otherwise known as cyclooxygenase-2 (COX-2) and are
15 therefore of use in therapy. Pro-inflammatory mediators of the cyclooxygenase pathway derived from arachidonic acid are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators such as prostaglandins, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety
20 of disease states and conditions. In particular these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors, or edema. Accordingly additional p38 mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by
25 cancer.

As a result of their p38 inhibitory activity, compounds of the invention have utility in the prevention and treatment of diseases associated with cytokine production including but not limited to those diseases associated with TNF,
30 IL-1, IL-6 and IL-8 production.

Thus TNF mediated diseases or conditions include for example rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoiiosis, bone resorption disease, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, AIDS, ARC or malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, viral infections such as HIV, CMV, influenza and herpes; and veterinary viral infections, such as lentivirus infections, including but not limited to equine infectious anemia virus, caprine arthritis virus, visna virus or maedi virus; or retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus or canine immunodeficiency virus.

Compounds of the invention may also be used in the treatment of viral infections, where such viruses elicit TNF production *in vivo* or are sensitive to upregulation by TNF. Such viruses include those that produce TNF as a result of infection and those that are sensitive to inhibition, for instance as a result of decreased replication, directly or indirectly by the TNF inhibiting compounds of the invention. Such viruses include, but are not limited to, HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses such as Herpes Zoster and Herpes Simplex.

IL-1 mediated diseases or conditions include for example rheumatoid arthritis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, stroke, endotoxemia and/or toxic shock syndrome, inflammatory reaction induced by endotoxin, diabetes, pancreatic β -cell disease, Alzheimer's disease, tuberculosis, atherosclerosis, muscle degeneration and cachexia.

IL-8 mediated diseases and conditions include for example those characterized by massive neutrophil infiltration such as psoriasis, inflammatory bowel disease, asthma, cardiac, brain and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and
5 glomerulonephritis. The increased IL-8 production associated with each of these diseases is responsible for the chemotaxis of neutrophils into inflammatory sites. This is due to the unique property of IL-8 (in comparison to TNF, IL-1 and IL-6) of promoting neutrophil chemotaxis and activation. Therefore, inhibition of IL-8 production would lead to a direct reduction in
10 neutrophil infiltration.

It is also known that both IL-6 and IL-8 are produced during rhinovirus (HRV) infections and contribute to the pathogenesis of the common cold and exacerbation of asthma associated with HRV infection [Turner *et al*, Clin.
15 Infec. Dis., 1997, 26, 840; Grunberg *et al*, Am. J. Crit. Care Med. 1997, 155, 1362; Zhu *et al*, J. Clin. Invest. 1996, 97, 421]. It has also been demonstrated *in vitro* that infection of pulmonary epithelial cells (which represent the primary site of infection by HRV) with HRV results in production of IL-6 and IL-8 [Sabauste *et al*, J. Clin. Invest. 1995, 96, 549]. Therefore, p38 inhibitors
20 of the invention may be used for the treatment or prophylaxis of the common cold or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus or adenovirus infection.

25 For the prophylaxis or treatment of a p38 or pro-inflammatory cytokine mediated disease the compounds according to the invention may be administered to a human or mammal as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or
30 more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

5

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

25

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

30

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or

multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds for use according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively the compounds for use according to the present invention may be formulated in a suitable

lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

5

For ophthalmic administration the compounds for use according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH adjusted sterile saline, either with or without a preservative such as bactericidal or fungicidal agent, for example
10 phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds for use according to the present
- 15 invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include for example cocoa butter, beeswax and polyethylene
20 glycols.

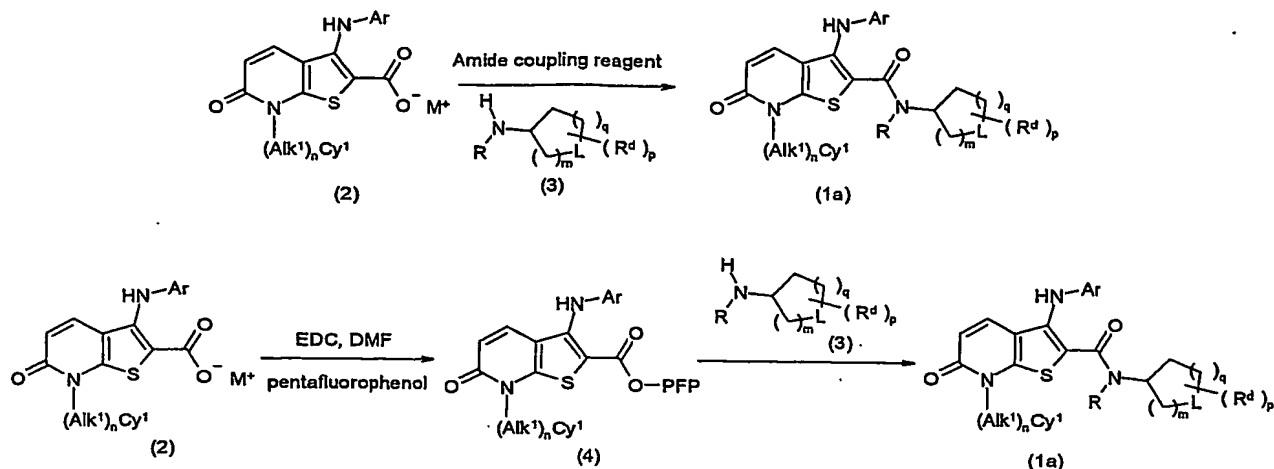
The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however,
25 daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

30

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar, Cy¹, Alk¹, n, R, R^d, p, m, q, Y and L when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention a compound of formula (1) in which Y is a -C(O)- group may be prepared from a carboxylic acid of formula (2) or ester of formula (5) according to amide bond forming reactions well known to those skilled in the art. Such reactions are set forth in references such as March's Advanced Organic Chemistry (John Wiley and Sons 1992), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1992) and Comprehensive Organic Functional Group Transformations, Ed. Katritzky et al, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon). Examples of such methods that may be employed to give compounds of formula (1a) are set out, but not limited to, the reactions in Scheme 1 and Scheme 2 below.

Scheme 1

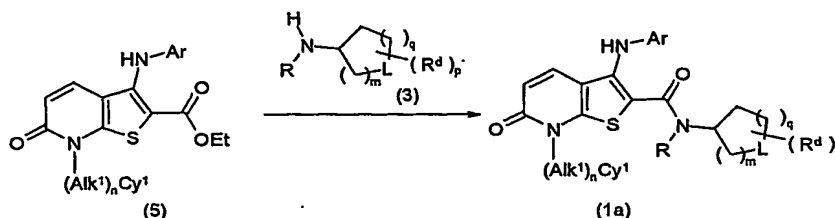


Thus amides of formula (1a) may be formed by reaction of a carboxylate salt of formula (2) [where M^+ is metal counter ion such as a sodium or lithium ion or is alternatively an ammonium or trialkylammonium counter ion] with an amine of formula (3) in the presence of a coupling reagent such as a carbodiimide e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) or N,N'-dicyclohexylcarbodiimide optionally in the presence of a base such as an amine e.g. triethylamine or N-methylmorpholine. These reactions may be performed in a solvent such as an amide solvent e.g. N,N-dimethylformamide (DMF) or an ether e.g. a cyclic ether such as tetrahydrofuran or 1,4-dioxane or a halogenated solvent such as dichloromethane at around ambient temperature to 60°C. In another procedure a pentafluorophenyl ester of formula (4) may be prepared by reaction of a carboxylic acid of formula (2) with pentafluorophenol in the presence of a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide in a solvent such as an amide solvent e.g. DMF at around ambient temperature. Amides of formula (1a) can then be prepared by reaction of the pentafluorophenyl ester with amines of formula (3) in an organic solvent such as a halogenated hydrocarbon e.g. dichloromethane at around ambient temperature. The intermediate acids of formula (2) may be prepared by hydrolysis of esters of formula (5) using a base such as an alkali metal hydroxide e.g. sodium hydroxide or lithium

hydroxide in water and a solvent such as tetrahydrofuran or an alcohol such as ethanol at a temperature from around ambient to reflux.

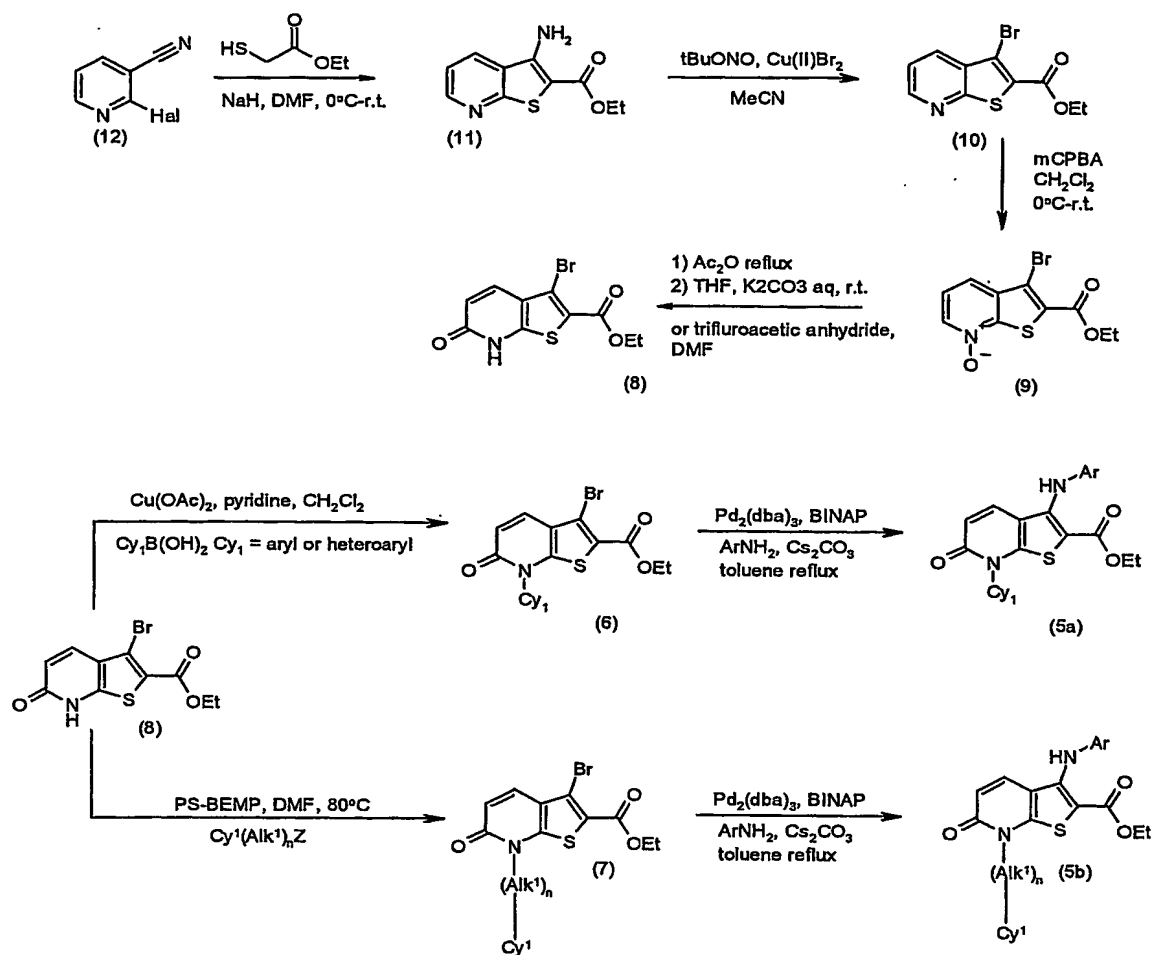
Amides of formula (1a) can also be prepared directly from esters of formula (5) by heating with an amine of formula (3) up to the reflux temperature of the amine optionally in the presence of a solvent such as 2-ethoxyethanol either at atmospheric pressure or under pressure in a sealed tube (Scheme 2)

Scheme 2



The intermediate esters of formula (5) may be prepared by the methods set out in Scheme 3 below. In the Scheme the preparation of an ethyl ester is specifically shown, but it will be appreciated that other esters may be obtained by simply varying the ester starting material and if appropriate any reaction conditions:

Scheme 3



Thus in Scheme 3 a compound of formula (5a) or (5b) may be prepared by reaction of a compound of formulae (6) or (7) with an amine ArNH_2 in the presence of a palladium catalyst. The reaction may be conveniently carried out in a solvent such as toluene at an elevated temperature, eg the reflux temperature, using a catalyst such as tris(dibenzylideneacetone)dipalladium(0), a phosphine ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and a base such as caesium carbonate. Where desired, alternative reaction conditions may be used, for example as described in the literature [Luker et al. Tet. Lett. (2001) 41, 7731; Buchwald S.L. J.Org.Chem. (2000) 65 1144; Hartwig J.F. Angew. Chem. Int. Ed. Engl. (1998) 37, 2046].

Intermediates of formula (7) may be prepared by reaction of a compound of formula (8) with an alkylating agent of formula $Cy^1(Alk^1)_nZ$, where Z is a leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy e.g. phenylsulphonyloxy group.

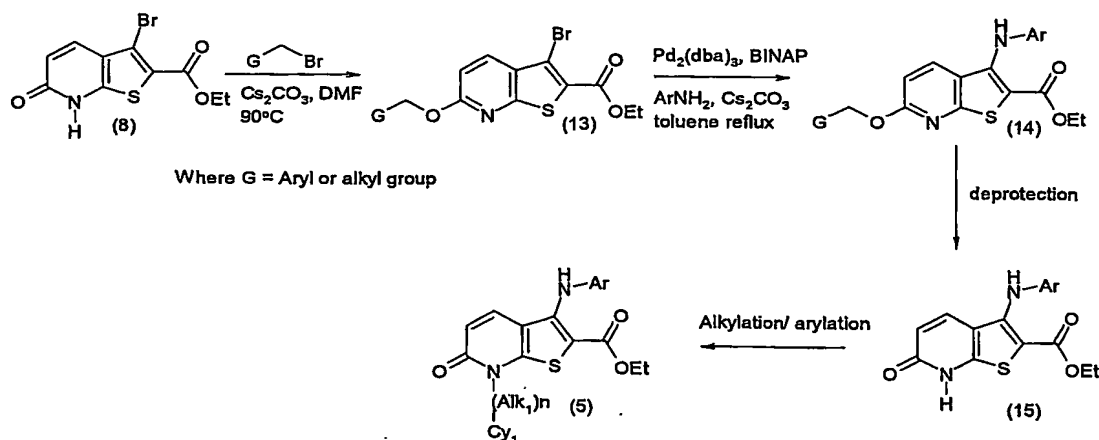
The reaction may be performed in the presence of a solvent, for example a substituted amide such as dimethylformamide, optionally in the presence of a base, for example an inorganic base such as sodium hydride, or an organic base such as an organic amine, e.g. a cyclic amine such as 1,5-diazabicyclo[4.3.0]non-5-ene or a resin bound organic amine such as resin bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP), at an elevated temperature, for example 80 to 100°C.

Intermediates of formula (6) may be prepared by the reaction of a compound of formula (8) with a boronic acid of formula $Cy^1B(OH)_2$ in which Cy^1 is an aryl or heteroaryl group. The reaction may be performed in an organic solvent, for example a halogenated hydrocarbon such as dichloromethane or dichloroethane in the presence of a copper reagent, for example a copper (I) salt such as CuI or for example a copper (II) reagent such as copper (II) acetate, optionally in the presence of an oxidant, for example 2,2,6,6-tetramethylpiperidine-1-oxide or pyridine-N-oxide, optionally in the presence of a base, for example an organic amine such as an alkylamine, e.g. triethylamine or an aromatic amine, e.g. pyridine at a temperature from around ambient to the reflux temperature [see for example Chan, D.T. *et al*/Tetrahedron Letters, 1998, 2933; Lam, P.Y.S. *et al*, Tetrahedron Letters, 2001, 3415]

Intermediates of formula (6) where Cy^1 is an aryl or heteroaryl group may also be prepared by nucleophilic aromatic substitution of a suitably activated aryl or heteroaryl halide with a compound of formula (8). The reaction may be performed in a dialkylamide solvent such as DMF in the presence of a base such as a metal hydride e.g. sodium hydride at a temperature from around ambient to 100°C. Suitably activated aryl or heteroaryl halides are those with an electron withdrawing substituent such as a nitro, cyano or ester group e.g. a chloro- or fluoro-nitrobenzene or 2-chloro-5-nitropyridine. Alternatively a nitrogen containing heteroaryl halide can be activated to nucleophilic substitution by N-oxidation e.g. 2-chloropyridine N-oxide.

It will be appreciated that if desired the reactions just described may be carried out in the reverse order so that the amination using $ArNH_2$ is performed first with the intermediate of formula (8) followed by alkylation/arylation to yield the compound of formula (5). It may be necessary to protect the nitrogen function of compounds of formula (8) during the course of these reactions. Such protection may be achieved by O-alkylation with an alkyl halide e.g. cyclopropylmethyl bromide or an arylalkyl bromide e.g. benzyl bromide as shown in Scheme 4.

20 Scheme 4



The O-alkylation reaction may be performed in an organic solvent such as DMF in the presence of a base, for example an inorganic base such as

Cs₂CO₃ or an organic base such as an amine e.g. a cyclic amine such as 1,5-diazabicyclo[4.3.0]non-5-ene at an elevated temperature e.g. 80 to 100°C to give a compound of formula (13). Reaction of the protected compound (13) with ArNH₂ under palladium catalysis can then be performed as previously described to give a compound of formula (14). Deprotection can then be achieved by treating a solution of this compound in an alcohol e.g. MeOH with a mineral acid such as concentrated HCl at an elevated temperature e.g. the reflux temperature to give a compound of formula (15). Alternatively when benzyl protection is employed then this group may be removed reductively by treating a solution of compound (14) in an organic solvent such as EtOH using a palladium or platinum catalyst e.g. palladium on carbon or PtO₂ under an elevated pressure of hydrogen at a temperature from around ambient to 60°C. Compounds of formula (15) can then undergo alkylation/arylation reactions as previously described to give compounds of formula (5).

Intermediate pyridinones of formula (8) may be prepared from pyridine N-oxides of formula (9) by sequential reaction with an anhydride, for example acetic anhydride at an elevated temperature, for example the reflux temperature followed by reaction with an inorganic base, for example a carbonate such as aqueous potassium carbonate in a solvent such as an ether for example a cyclic ether e.g. tetrahydrofuran at around ambient temperature. Alternatively the reaction may be performed using trifluoroacetic anhydride in dimethylformamide from 0°C to ambient temperature conditions [see for example Konno et al., Heterocycles (1986) 24, 2169].

Pyridine N-oxides of formula (9) may be formed by oxidation of pyridines of formula (10) using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid or m-chloroperoxybenzoic acid in a solvent, such as a

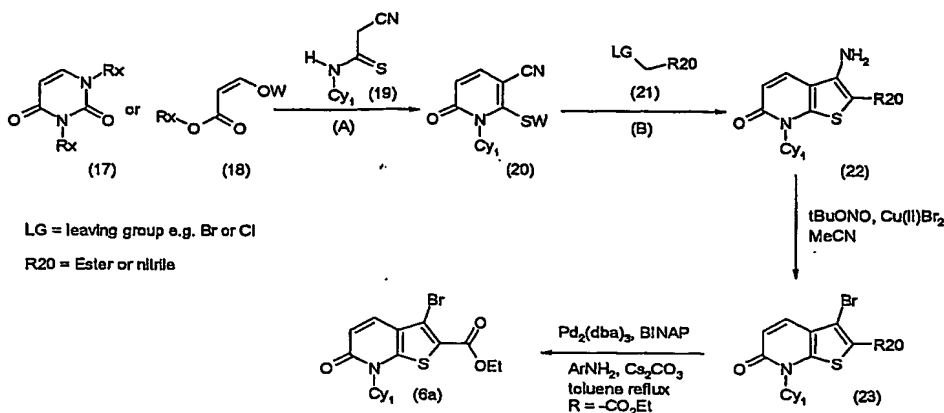
halogenated hydrocarbon e.g. dichloromethane or an alcohol e.g. tert-butanol at a temperature from the ambient temperature to the reflux temperature.

Intermediate pyridines of formula (10) in Scheme 3 may be obtained by standard methods such as for example by the Sandmeyer reaction. Thus for example a bromide of formula (10) may be prepared by treatment of an aryl amine of formula (11) with an alkyl nitrite, for example t-butyl nitrite and a copper salt, for example copper (II) bromide in the presence of a solvent, for example a nitrile such as acetonitrile at a temperature from about 0°C to around 65°C.

Amines of formula (11) may be formed from 2-halopyridine-3-carbonitriles of formula (12) by reaction with a reagent such as ethyl 2-mercaptoacetate. The reaction may be performed in the presence of a solvent such as a substituted amide for example dimethylformamide or an ether e.g. a cyclic ether such as tetrahydrofuran or alcohol such as ethanol in the presence of a base, for example an inorganic base such as sodium carbonate or a hydride e.g. sodium hydride or an organic base such as 1,5-diazabicyclo[4.3.0]non-5-ene or a trialkylamine such as triethylamine at a temperature between about 0°C and 100°C. The carbonitrile starting materials are readily available or may be obtained from known compounds using standard procedures.

In another process intermediate esters of formula (6a) may be prepared by the reactions set out in Scheme 5. In the Scheme below R²⁰ represents an ester or nitrile and LG represents a leaving group such as a halogen e.g. chlorine or bromine or sulfonyloxy group such as an alkylsulfonyloxy group e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy group e.g. p-toluenesulfonyloxy group.

Scheme 5



Thus in step (A) of the reaction scheme a compound of formulae (17) or (18), where Rx is an optionally substituted alkyl group e.g. methyl and W is a hydrogen atom metal ion or amine salt, may be reacted with a thioamide of formula (19). The reaction may be performed in the presence of a base. Appropriate bases may include, but are not limited to, lithium bases such as n-butyl or t-butyl lithium or lithium diisopropylamide (LDA), or silazanes e.g. lithium hexamethyldisilazane (LiHMDS) or sodium hexamethyldisilazane (NaHMDS), or a carbonate, e.g. potassium carbonate, an alkoxide, e.g. sodium ethoxide, sodium methoxide, potassium t-butoxide, a hydroxide e.g. NaOH or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine, such as N-methylmorpholine or pyridine. The reaction may be performed in an organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol, ethanol or propanol or acetonitrile, at a temperature from ambient to the reflux temperature. In one particular aspect of the process the reaction is achieved using an alkoxide base, especially sodium ethoxide or sodium methoxide in an alcoholic solvent, especially ethanol at reflux temperature.

Intermediates of formula (17), where not commercially available, may be prepared using standard methodology. (See, for example, Mir Hedayatullah, J. Heterocyclic Chem., 18, 339, (1981)). Similarly, intermediates of formula

(18) where not commercially available, may be prepared using standard methodology. For example they may be prepared *in-situ* by reaction of an acetate e.g. ethyl acetate with a base such as sodium methoxide followed by addition of a formate e.g. methyl formate.

5

In a similar manner, Intermediates of formula (19), if not commercially available, may be prepared using methods known to those skilled in the art (see, for example Adhikari et al, Aust. J. Chem., 52, 63-67, (1999)). For example, an isothiocyanate of formula Cy^1NCS may be reacted with
10 acetonitrile in the presence of a base e.g. NaHMDS in a suitable solvent e.g. tetrahydrofuran, optionally at a low temperature, e.g. around $-78^{\circ}C$. According to the nature of the group Cy^1 , the Intermediate of formula (19) may be prepared *in situ*, for example, using the methods as described herein, followed by subsequent addition of a compound of formulae (17) or (18).

15

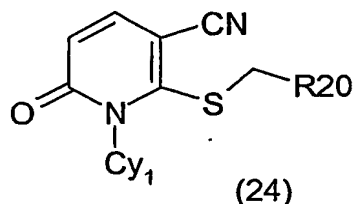
During the course of this process an intermediate of formula (20) may be formed. If desired the intermediate may be isolated at the end of step (A) and subsequently reacted with intermediate (21) to form the desired amine (22). In some instances however it may advantageous not to isolate the
20 intermediate of formula (20) and reaction (B) may be carried out directly with the reaction mixture of step (A).

If a different solvent is used during the second stage of the process, it may be necessary to evaporate the solvent, *in vacuo*, from the first stage of the
25 process before proceeding with the second stage. Once evaporated, the crude solids from step (A) may be used in the next stage or they may be purified, for example, by crystallisation, to yield an isolated intermediate, such as a compound of formula (20).

30 During step (B) of the process an intermediate of formula (21) may then be added to the reaction mixture or to the crude solids or purified product from

step (A) in a suitable solvent. Suitable solvents include, but are not limited to, amides e.g. a substituted amide such as dimethylformamide, alcohols e.g. ethanol, methanol or isopropyl alcohol, ethers e.g. a cyclic ether such as tetrahydrofuran or dioxane or acetonitrile. The reaction may be performed at a temperature from ambient up to the reflux temperature.

During the course of step (B) an intermediate of formula (24):



may be observed or even isolated, depending upon the nature of the group R^{20} . The intermediate of formula (24) may be converted to a compound of formula (22) using the methods described above. In this situation it may be necessary to add a base, in order for the reaction to proceed to completion. Appropriate bases include carbonates e.g. caesium or potassium carbonate, or alkoxides e.g. potassium *t*-butoxide, or hydrides e.g. sodium hydride or organic amines e.g. triethylamine or *N,N*-diisopropylethylamine or cyclic amines, such as *N*-methylmorpholine or pyridine.

Amines of formula (22) can be converted to bromides of formula (23) by standard methods such as for example by the Sandmeyer reaction as previously described for compounds of formula (11). Compounds of formula (6a) can then be prepared from these bromides by the palladium catalysed amination reactions already described.

It will be appreciated that Intermediates of formula (21) where not commercially available may be prepared using standard methods known to those skilled in the art. For example, alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups using conditions

known to the skilled artisan. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon e.g., dichloromethane to yield the corresponding chloride. A base e.g., triethylamine may also be used in the reaction.

5

It will be appreciated that in Scheme 5 when R20 is nitrile that a compound of formula (23a) may be prepared. Such nitriles are useful intermediates in the synthesis of intermediate carboxylic acids of formula (25a). This reaction may be performed by hydrolysis of the nitrile (23a) with a base such as an alkali metal hydroxide e.g. an 2M aqueous solution of sodium hydroxide in an alcohol solvent such as methanol or ethanol at reflux.

10



15

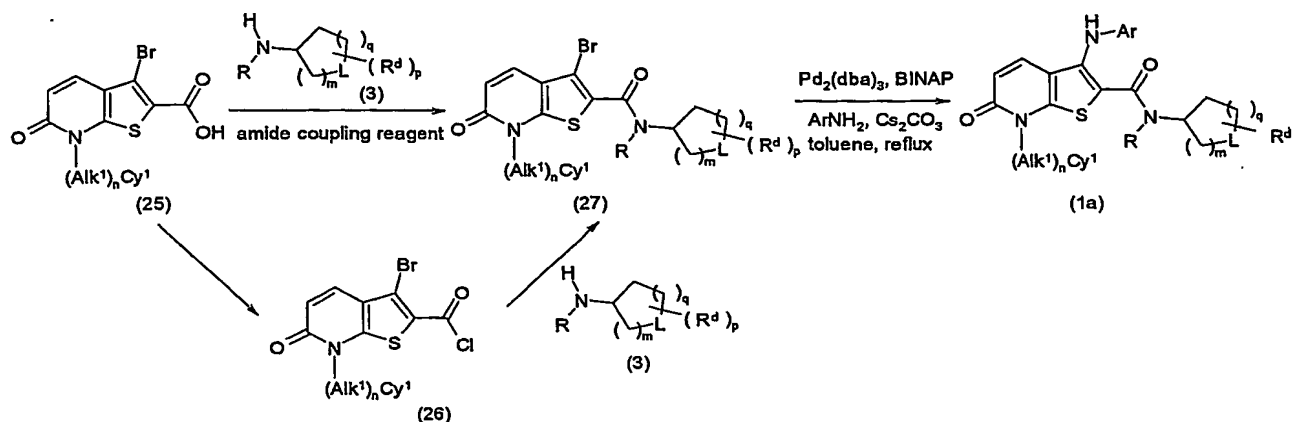
It will be appreciated that intermediates, such as intermediates (17), (18), (19) or (21), if not available commercially, may also be prepared by methods known to those skilled in the art following procedures set forth in references such as Rodd's Chemistry of Carbon Compounds, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-19 (John Wiley and Sons, 1999), Comprehensive Heterocyclic Chemistry, Ed. Katritzky et al, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), Comprehensive Organic Functional Group Transformations, Ed. Katritzky et al, Volumes 1-7, 1995 (Pergamon), Comprehensive Organic Synthesis, Ed. Trost and Fleming, Volumes 1-9, (Pergamon, 1991), Encyclopedia of Reagents for Organic Synthesis Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989) and March's Advanced Organic Chemistry (John Wiley and Sons, 1992).

20

25

In another process amides of formula (1a) may be prepared by the reactions detailed in Scheme 6 below.

Scheme 6

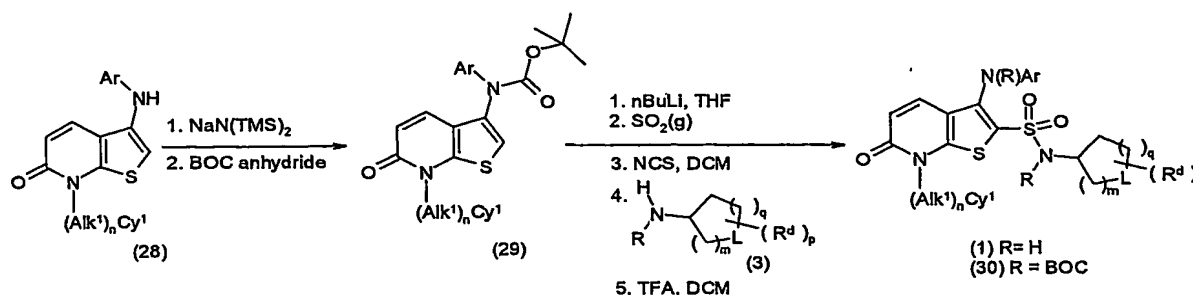


- 5 Thus acids of formula (25) or (25a) may be converted to amides of formula (27) by reaction with amines of formula (3) in the presence of coupling reagents in the same way as previously described for the conversion of compounds (2) to amides of formula (1a). Alternatively the carboxylic acids
- 10 may be converted to acid chlorides of formula (26) by reaction with a chlorinating agent such as oxalyl chloride optionally in the presence of a catalytic amount of DMF in a solvent such as a halogenated hydrocarbon e.g. dichloromethane or an ether e.g. a cyclic ether such as tetrahydrofuran at around ambient temperature. The resultant acid chlorides may then be
- 15 reacted with amines of formula (3) in a solvent such as a halogenated hydrocarbon e.g. dichloromethane in the presence of an amine base such as triethylamine at around ambient temperature to give amides of formula (27). Amides of formula (1a) may then be prepared from amides of formula (27) using a palladium catalysed arylation procedure previously described in
- 20 Scheme 1. During the course of the reactions described above it may be advantageous or necessary to protect the R^d substituents that may be present. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances,

deprotection may be the final step in the synthesis of a compound of formula (1a) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

- 5 According to a further aspect of the invention a compound of formula (1) in which Y is an $-S(O_2)-$ group may be prepared by the route set out in Scheme 7.

Scheme 7



Thus a compound of formula (29) can be obtained by reaction of a compound of formula (28) with a metal amide base such as sodium bis(trimethylsilyl)amide in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran at a temperature of around $0^\circ C$ and then adding di-*tert*-butyl dicarbonate in a solvent such as tetrahydrofuran and stirring at ambient temperature. A compound of formula (1) can then be prepared by the following reaction sequence. A compound of formula (29) is treated with a base such as an alkyl lithium, e.g. *n*-butyl lithium in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran at a temperature of around $-78^\circ C$. Sulfur dioxide gas is bubbled through the reaction mixture before allowing the reaction to warm to room temperature. Solvents are removed *in vacuo* and the crude material dissolved in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane and the mixture treated with a chlorinating reagent such as *N*-chlorosuccinimide at around ambient temperature. An amine of formula (3) can then be added to the reaction mixture to produce a compound of formula (30), where $R = t$ -butoxycarbonyl.

A sulphonamide of formula (1) can then be prepared by treating a compound of formula (30) with an acid e.g. a mineral acid such as HCl or an organic acid such as trifluoroacetic acid in a solvent such as a halogenated hydrocarbon e.g. dichloromethane. Intermediates of formula (28) may be
5 obtained by decarboxylation of compounds of formula (2) with an acid such as a mineral acid e.g. HCl in a solvent such as an ether e.g. a cyclic ether e.g. tetrahydrofuran or 1,4-dioxane at a temperature from 50°C up to the reflux temperature.

10 Where in the general processes described above intermediates such as alkylating agents of formula $Cy^1(Alk^1)_nZ$, reagents of formula $HXCH_2CO_2Et$ and any other intermediates required in the synthesis of compounds of the invention are not available commercially or known in the literature, they may be readily obtained from simpler known compounds by one or more standard
15 synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other
20 intermediates and in particular compounds of formula (1) where appropriate functional groups exist in these compounds. Particular examples of such methods are given in the Examples hereinafter.

Thus for example aromatic halogen substituents in the compounds may be
25 subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile, a
30 thiomethyl group may be introduced by using dimethyldisulphide as the electrophile, an alcohol group may be introduced by using an aldehyde as

electrophile and an acid may be introduced by using carbon dioxide as electrophile. Aromatic acids of formula ArCO_2H may also be generated by quenching Grignard reagents of formula ArMgHal with carbon dioxide.

- 5 Aromatic acids of formula ArCO_2H generated by this method and acid containing compounds in general may be converted to activated derivatives, e.g. acid halides by reaction with a halogenating agent such as a thionyl halide e.g. thionyl chloride, a phosphorous trihalide such as phosphorous trichloride or a phosphorous pentahalide such as phosphorous pentachloride
- 10 optionally in an inert solvent such as an aromatic hydrocarbon e.g. toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to the reflux temperature, or may be converted into Weinreb amides of formula $\text{ArC}(\text{O})\text{N}(\text{OMe})\text{Me}$ by conversion to the acid halide as just described and subsequent reaction with an amine of formula $\text{HN}(\text{OMe})\text{Me}$ or a salt
- 15 thereof, optionally in the presence of a base such as an organic amine, e.g. triethylamine in an inert solvent such as an aromatic hydrocarbon e.g. toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to ambient temperature.
- 20 Ester groups such as $-\text{CO}_2\text{Alk}^6$ and $-\text{CO}_2\text{R}^4$ in the compound of formula (1) and intermediates thereto may be converted to the corresponding acid [$-\text{CO}_2\text{H}$] by acid- or base-catalysed hydrolysis depending on the nature of the group Alk^6 or R^4 . Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic
- 25 acid in an organic solvent e.g. dichloromethane or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

- In a further example, $-\text{OR}^6$ [where R^6 represents an alkyl group such as
- 30 methyl group] in compounds of formula (1) and intermediates thereto may be cleaved to the corresponding alcohol $-\text{OH}$ by reaction with boron tribromide in

a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C .

Alcohol [-OH] groups may also be obtained by hydrogenation of a
5 corresponding $-\text{OCH}_2\text{R}^{31}$ group (where R^{31} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [e.g. -
10 CO_2Alk^6] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted
15 to a corresponding $-\text{OR}^6$ group by coupling with a reagent R^6OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

20 Aminosulphonylamino [-NHSO₂NH₂] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [-NH₂] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

25 In another example compounds containing a $-\text{NHCSR}^7$ or $-\text{CSNHR}^7$ group may be prepared by treating a corresponding compound containing a $-\text{NHCOR}^7$ or $-\text{CONHR}^7$ group with a thiation reagent, such as Lawesson's Reagent or P_2S_5 , in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

30

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a reducing agent. Suitable reducing agents include borohydrides for example sodium triacetoxyborohydride or sodium cyanoborohydride. The reduction may be carried out in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Alternatively, the amine and aldehyde may be initially reacted in a solvent such as an aromatic hydrocarbon e.g. toluene and then subjected to hydrogenation in the presence of a metal catalyst, for example palladium on a support such as carbon, in a solvent such as an alcohol, e.g. ethanol.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) and intermediates thereto may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine ($-CH_2NH_2$) groups in compounds of formula (1) and intermediates thereto may be obtained by reduction of nitriles ($-CN$), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney[®] nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran or an alcohol e.g. methanol or ethanol, optionally in

the presence of ammonia solution at a temperature from ambient to the reflux temperature, or by chemical reduction using for example a metal hydride e.g. lithium aluminium hydride, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from 0°C to the reflux temperature.

5

In another example, sulphur atoms in the compounds, for example when present in a group L¹ or L² may be oxidised to the corresponding sulfoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

10

In a further example N-oxides of compounds of formula (1) may in general be prepared for example by oxidation of the corresponding nitrogen base as described above in relation to the preparation of intermediates of formula (5).

15

Salts of compounds of formula (1) may be prepared by reaction of compounds of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

20

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

25

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and

30

the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C.

The following abbreviations are used:

NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
MeOH - methanol;	BOC - butoxycarbonyl;
DCM - dichloromethane;	AcOH - acetic acid;
DIPEA - diisopropylethylamine;	EtOH - ethanol;
Pyr - pyridine;	Ar - aryl;
DMSO - dimethylsulphoxide;	iPr - isopropyl;
Et ₂ O - diethylether;	Me - methyl;
THF - tetrahydrofuran;	h - hour;
MCPBA - 3-chloroperoxybenzoic acid;	NBS - N-bromosuccinimide;
Fmoc - 9-fluorenylmethoxycarbonyl;	r.t. - room temperature;
DBU - 1,8-Diazabicyclo[5,4,0]undec-7-ene;	
EDC - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride;	
HOBT - 1-hydroxybenzotriazole hydrate;	

BINAP - 2,2'-bis(diphenylphosphino)-1-1'-binaphthyl;

DMF - N,N-dimethylformamide;

DME - Ethylene glycol dimethyl ether

p.s.i. - pounds per square inch

5 MTBE – methyl *tert*-butylether

All NMRs were obtained either at 300MHz or 400MHz.

10 Compounds were named with the aid of either Beilstein Autonom supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany or ACD Labs Name (v.6.0) supplied by Advanced Chemical Development, Toronto, Canada.

15 LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100 LC/MS using the following following method: Phenomenex Luna 3 μ C₁₈(2) 50x4.6mm column; mobile phase A = 0.1% formic acid in water; mobile phase B = 0.1% formic acid in MeCN; flow rate of 0.9mLmin⁻¹, column temperature 40°C.

20

Gradient:-

Time (minutes)	%B	%A
Initial	5	95
2.0	95	5
3.0	95	5
5.0	5	95
5.5	end	end

Where stated alternative LCMS conditions (Conditions B) were used:

LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100/ThermoFinnigan LCQ Duo LC/MS system using Electrospray ionisation and the following LC method: Phenomenex Luna C₁₈(2) 5 μ 100mm x 4.6mm column; mobile phase A = 0.08% formic acid in water; mobile phase B = 0.08% formic acid in MeCN; flow rate of 3.0 mLmin⁻¹, column temperature 35°C.

Gradient:-

Time (min)	%A	%B
0.00	95.0	5.0
4.40	5.0	95.0
5.30	5.0	95.0
5.32	95.0	5.0
6.50	95.0	5.0

Intermediate 1

Ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of 2-chloro-3-cyanopyridine (330g, 2.3mol), ethyl 2-mercaptoacetate (361.2g, 3.0mol), sodium carbonate (265g, 2.5mol) and EtOH (1.2L) was heated to reflux for 4.5 hours. The reaction mixture was cooled to ambient temperature and added to water (15L). The resultant precipitate was stirred for 30 minutes and then filtered. The filter cake was washed with two portions of water (2 x 2.5L) and dried to constant weight under vacuum at 45°C to yield the title compound as a brown solid (493.1g, 93.2%). δ H (CDCl₃) 8.68 (1H, dd, \underline{J} 4.7, 1.2Hz), 7.93 (1H, dd, \underline{J} 8.5, 1.2Hz), 7.29 (1H, dd, \underline{J} 8.5, 4.7Hz), 5.90 (2H, b), 4.38 (2H, q, \underline{J} 7.0Hz), 1.40 (3H, t, \underline{J} 7.0Hz). LCMS RT 2.9 minutes, 223 (M+H)⁺

Intermediate 2

Ethyl 3-bromothieno[2,3-b]pyridine-2-carboxylate

Intermediate 1 (363.6g) was added in portions over two hours to a mixture of copper(II) bromide (403.3g), t-butyl nitrite (220.6g) and acetonitrile (3.6L) stirred at a temperature of 20 to 25°C. The mixture was stirred at 20°C for 2 hours before it was slowly added to 2M HCl(aq) (4.2L). The reaction mixture slurry was filtered and the solids were washed with water (500mL). The combined filtrate was extracted with ethyl acetate (8L), this ethyl acetate solution was washed with 2M HCl(aq) (2.2L). The solids were dissolved in ethyl acetate (6L), this solution was washed twice with 2M HCl(aq) (4.4L and 2.2L). The two ethyl acetate solutions were then combined and washed with 2M HCl(aq) (2.2L) and twice with water (2 x 2L). The ethyl acetate solution was then dried (MgSO₄), filtered and concentrated *in vacuo* at 40 mbar and 60°C to give a solid residue. This was broken up and dried to constant weight under vacuum at 45°C to yield the title compound as a brown solid (458.5g, 97.9%). δ H (DMSO-d₆) 8.89 (1H, d, J 4.7Hz), 8.47 (1H, d, J 8.6Hz), 7.71 (1H, dd, J 8.6, 4.7Hz), 4.46 (2H, q, J 7.2Hz), 1.40 (3H, t, J 7.2Hz). LCMS RT 3.8 minutes, 288 (M+H)⁺

20 Intermediate 3

Ethyl 3-Bromothieno[2,3-b]pyridine-2-carboxylate N-oxide

To a slurry of Intermediate 2 (214g, 0.747mol) in DCM (2140mL) under nitrogen was added 70% mCPBA (240g, 0.97mol) portion wise over 0.5h. The reaction was then stirred at room temperature for 18h. The reaction mixture was quenched with water (800mL) and pH adjusted to 8.5 with 10%w/v sodium carbonate solution (1250mL). The basic aqueous layer was removed and the organic layer washed with water until pH 7. The organic layer was concentrated *in vacuo* and the crude title product was recovered as a tan solid. The crude product was purified by slurrying in MTBE (600mL) for 1h at 0-5°C to give the title compound (174g, 77%). δ H (CDCl₃) 8.44 (1H, dd, J 6.2, 0.8Hz), 7.87 (1H, dd, J 8.3, 0.8Hz), 7.48 (1H, dd, J 8.3, 6.2Hz), 4.49

(2H, q, \underline{J} 7.1Hz), 1.48 (3H, t, \underline{J} 7.1Hz). LCMS (ES⁺) RT 2.61 minutes, 302(M+H)⁺

5 Intermediate 4

Ethyl 3-bromo-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

To a suspension of Intermediate 3 (95g, 0.32mol) in DMF (950mL) and stirred at room temperature was added trifluoroacetic anhydride (198g, 131mL, 0.94mol) drop wise over a 30 minute period (slight exotherm observed). After complete addition the reaction was stirred for a further 45 minutes at room temperature. The excess trifluoroacetic anhydride was removed under vacuum and the reaction mixture concentrated to approximately half the original volume. The resulting dark coloured solution was then poured onto a mixture of water (1L) toluene (400mL). The mixture was left to stand for around 10 minutes and then the precipitate was collected by filtration. The precipitate was washed with toluene (3 X 50mL) and then dried in a vacuum oven at 50-60°C. This gave the title compound as a beige coloured solid (68.5g, 72.1%). δ H (DMSO-d₆) 12.20 (1H, brs), 7.75 (1H, d, \underline{J} 9.0Hz), 6.50 (1H, d, \underline{J} 9.0Hz), 4.15 (2H, q, \underline{J} 7.1Hz), 1.12 (3H, t, \underline{J} 7.1Hz). LCMS (ES⁺) RT 2.86 minutes, 302 ((M+H)⁺, 100%). M.p. 261.7-268.1°C.

Intermediate 5 (Method A)

Ethyl 3-bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

A 3L jacketed vessel was charged with Intermediate 4 (100g, 0.332mol), CuI (15.8g, 0.083mol), phenylboronic acid (80g, 0.664mol), pyridine (104g, 1.32mol) and acetonitrile (2.0L) and the mixture stirred at 40°C. Compressed air was vigorously blown through the reaction mixture for 6 hours. The compressed air was then turned off and the reaction mixture left to stir at 40°C overnight. The next day the same process was repeated. After approximately 36 hours, HPLC indicated >97% conversion of starting

material to the product. The resulting dark coloured reaction mixture was poured onto a mixture of water (1.2L) and concentrated hydrochloric acid (300mL). The mixture was extracted with dichloromethane (2 X 1.5L) and the combined organics washed with 2M HCl(aq) (2 x 1.5L). The organic layer was separated, passed through a pad of MgSO₄, and concentrated *in vacuo*. The crude residue was recrystallised from toluene (600ml) to give the title compound as a beige solid (93.85g, 75.0%). δ H (CDCl₃) 7.82 (1H, d, \downarrow 8.5Hz), 7.70-7.62 (3H, m), 7.54-7.42 (2H, m), 6.70 (1H, d, \downarrow 8.5Hz), 4.15 (2H, q, \downarrow 7.1Hz), 1.14 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT 3.75 minutes, 378 (M+H)⁺. MP = 201.6-206.0°C

Intermediate 5 (alternative procedure Method B)

Ethyl 3-bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

To a 2 necked round bottomed flask was added in sequence Intermediate 4 (302mg, 1.00mmol), copper(II) acetate (278mg, 1.50mmol), phenylboronic acid (488mg, 4.00mmol), DCM (5mL) and pyridine (158mg, 2.00mmol). The reaction was stirred at room temperature for 18h with the exclusion of moisture. The reaction was then diluted with DCM (50mL), washed with 2M HCl(aq) (50mL), the aqueous was re-extracted with DCM (50mL). The combined organics were then washed with water (50mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by a slurry in methanol (12mL), to give the title compound as a beige solid (270mg, 72%). δ H (CDCl₃) 7.82 (1H, d, \downarrow 8.5Hz), 7.70-7.62 (3H, m), 7.54-7.42 (2H, m), 6.70 (1H, d, \downarrow 8.5Hz), 4.15 (2H, q, \downarrow 7.1Hz), 1.14 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT 3.75 minutes, 378 (M+H)⁺.

Intermediate 6

Ethyl 3-[(2,4-difluorophenyl)amino]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

Tris(dibenzylideneacetone)dipalladium(0) (1.21g, 1.32mmol) was added to a mixture of Intermediate 5 (10g, 26.4mmol), caesium carbonate (12.05g, 37.0mmol), 2,4-difluoroaniline (4.1g, 3.23mL, 31.7mmol) and BINAP (1.65g, 2.64mmol) in anhydrous toluene (80mL) and the reaction heated to reflux under nitrogen for 4 days. The reaction was cooled, partitioned between DCM and water and the organic phase dried (MgSO₄) and evaporated *in vacuo*. The crude residue was triturated with methanol to give the title compound as a white solid (9.87g) δ H (CDCl₃) 8.49 (1H, bs), 7.58-7.40 (3H, m), 7.32-7.25 (2H, m), 7.13-7.04(1H, m), 7.01 (1H, d, J 9.8Hz), 6.93-6.86 (1H, m), 6.82-6.75 (1H, m), 6.31 (1H, d, J , 9.8Hz), 4.20 (2H, q, J 7.1Hz), 1.23 (3H, J 7.1Hz). LCMS (ES⁺) RT 4.06 minutes, 427 (M+H)⁺.

Intermediate 7

Lithium 3-[(2,4-difluorophenyl)amino]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

A solution of lithium hydroxide monohydrate (686mg, 16.4mmol) in water (125mL) was added to a suspension of Intermediate 6 (6.34g, 14.9mmol) in ethanol (250mL) and THF (125mL). The reaction was stirred at 85°C for 4h before allowing to cool to room temperature. Solvent was removed *in vacuo* and the residue co-evaporated with toluene (3 x 50mL) to give the title compound as a brown solid (6.02g). δ H (DMSO-d₆) 10.04 (1H, bs), 7.81 (3H, m), 7.69 (2H, m), 7.50 (1H, m), 7.48 (1H, d, J 9.6Hz), 7.16 (2H, m), 7.56 (1H, d, J 9.6Hz).

Intermediate 8

Pentafluorophenyl 3-[(2,4-difluorophenyl)amino]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (3.42g, 17.8mmol) was added to a solution of Intermediate 7 (6.02g, 14.9mmol) in DMF (300mL). The reaction was stirred at room temperature for 30 minutes before adding pentafluorophenol (4.10g, 22.3mmol) and then stirred for a further 16h at r.t..

Solvent was removed *in vacuo* and the residue dissolved in DCM (150mL), washed with water (2 x 100mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 20-40% EtOAc in isohexane) to give the title compound as a white solid (1.71g). δ H (CDCl₃) 8.66 (1H, bs), 7.76 (3H, m), 7.58 (2H, m), 7.47 (1H, m), 7.14 (3H, m), 6.54 (1H, d, \downarrow 9.9Hz). LCMS (ES⁺) RT 4.57 minutes, 565 (M+H)⁺.

Example 1

3-[(2,4-Difluorophenyl)amino]-N-[(1R*,2S*)-2-hydroxycyclopentyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxamide

To a solution of Intermediate 8 (200mg, 0.354mmol) in DCM (4mL) was added *cis*-2-aminocyclopentanol hydrochloride (97mg, 0.709mmol) and diisopropylethylamine (0.14mL, 0.78mmol) and the reaction stirred at r.t. for 18h. A further equivalent of the aminocyclopentanol (48.5mg, 0.354mmol) and diisopropylethylamine (0.07mL, 0.39mmol) was added and the reaction stirred for a further 7h. Solvent was removed *in vacuo* and the residue purified by column chromatography (silica, 20-60% EtOAc in isohexane) to give the title compound as an off-white solid (115mg). δ H (CDCl₃) 8.75 (1H, s), 7.47-7.55 (3H, m), 7.32 (2H, m), 7.12 (1H, d, \downarrow 9.7Hz), 7.00-6.94 (1H, m), 6.89-6.83 (1H, m), 6.76 (1H, m), 6.36 (1H, d, \downarrow 9.7Hz), 5.94 (1H, d, \downarrow 6.7Hz), 4.09-4.04 (2H, m), 1.98-1.53 (4H, m), 1.51-1.41 (3H, m). LCMS (ES⁺) RT 3.32 minutes, 482 (M+H)⁺.

Example 2

3-[(2,4-Difluorophenyl)amino]-N-[(1R*,2R*)-2-hydroxycyclopentyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxamide

To a solution of Intermediate 8 (200mg, 0.354mmol) in DCM (4mL) was added *trans*-2-aminocyclopentanol (72mg, 0.709mmol) and the reaction stirred at r.t. for 18h. A further 3 equivalents of the aminocyclopentanol (108mg) were added and the reaction stirred for a further 24h. Solvent was removed *in vacuo* and the residue purified by column chromatography (silica,

50-100% EtOAc in isohexane) to give the title compound as a yellow solid (145mg, 85%). δ H (CDCl₃) 8.70 (1H, bs), 7.57-7.51 (3H, m), 7.34 (2H, m), 7.08 (1H, d, J 9.8Hz), 7.05-6.99 (1H, m), 6.91-6.86 (1H, m), 6.81-6.76 (1H, m), 6.36 (1H, d, J 9.8Hz), 5.51 (1H, d, J 4.1Hz), 3.93-3.86 (1H, m), 3.85-3.82 (1H, m), 2.06-2.00 (1H, m), 1.97-1.90 (1H, m), 1.75-1.68 (1H, m), 1.60-1.50 (1H, m), 1.30-1.20 (1H, m). LCMS (ES⁺) RT 3.24 minutes, 482 (M+H)⁺.

Preparation of activated human p38 α for inhibitor assays.

10

Purification of human p38 α

Human p38 α , incorporating an N-terminal (His)6 tag, was expressed in baculovirus-infected High-Five™ cells (Invitrogen) according to the manufacturers instructions. The cells were harvested 72h post-infection and
15 lysed in phosphate buffered saline (PBS) containing 1% (w/v) β -octylglucoside and Complete, EDTA-free™ protease inhibitors (Roche Molecular Biochemicals). The lysate was centrifuged at 35000xg for 30min at 4oC and the supernatant applied to a NiNTA™ column (Qiagen). Bound protein was eluted by 150mM imidazole in PBS (after a wash with 15mM
20 imidazole in PBS) and directly applied to a HiTrap Q™ column (AP Biotech). Bound protein was eluted using a 20 column volume, 0 to 1M NaCl gradient. Fractions containing (His)6-p38 were aliquotted and stored at -70° prior to their activation.

25 Preparation of GST-MKK6EE-containing lysates

E. coli (BL21 pLysS) expressing the constitutively activated form of human MKK6 fused with an N-terminal glutathione-S-transferase tag (GST-MKK6EE) were harvested by centrifugation and frozen at -70°. Cells were lysed by resuspension in 1/10th the culture volume of PBS containing
30 Complete, EDTA-free™ protease inhibitors followed by sonication on ice for

4x15 sec. Cell debris was removed by centrifugation at 35,000xg and the resultant supernatant stored in aliquots at -70°.

Activation of (His)6-p38

5 0.45mL of purified (His)6-p38 was incubated with 50μL of the GST-MKK6EE-containing lysate for 30min at 23° in the presence of 1mM β-glycerophosphate, 10mM MgCl₂ and 9mM ATP. The extent of activation was monitored by mass spectrometric detection of the doubly-phosphorylated form of (His)6-p38, which routinely comprised greater than 90% of the final
10 (His)6-p38 preparation. The activated (His)6-p38 was then diluted x10 in PBS and repurified using the method described above. The concentration of purified, activated (His)6-p38 was measured by UV absorbance at 280nm using A₂₈₀, 0.1%=1.2 and the preparation stored in aliquots at -70° prior to its use in inhibitor assays.

15

p38 Inhibition Assays

Inhibition of phosphorylation of biotinylated myelin basic protein (MBP)

The inhibition of p38 catalysed phosphorylation of biotinylated MBP is measured using a DELFIA based format. The assay was performed in a
20 buffer comprising, 20mM HEPES (pH 7.4), 5mM MgCl₂ and 3mM DTT. For a typical IC₅₀ determination, biotinylated MBP (2.5μM) was incubated at room temperature in a streptavidin-coated microtitre plate together with activated gst-p38 (10nM) and ATP (1μM) in the presence of a range of inhibitor concentrations (final concentration of DMSO is 2 percent). After fifteen
25 minutes the reaction was terminated by the addition of EDTA (75mM). The microtitre plate was then washed with Tris buffered saline (TBS), prior to the addition of 100μl of anti-phospho MBP antibody (mouse) together with europium-labeled anti-mouse IgG antibody. After one hour at room temperature the plate was again washed in TBS followed by the addition of
30 Enhancement solution (PerkinElmer Wallac). Fluorescence measurements were performed after a further fifteen minutes at room temperature.

IC50 values are determined from the plot of Log₁₀ inhibitor concentration (x-axis) versus percentage inhibition of the fluorescence generated by a control sample in the absence of inhibitor (y-axis).

5 **Purification of human Peripheral Blood Mononuclear Cells**

Peripheral blood mononuclear cells (PBMC) were isolated from normal healthy volunteers. Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), diluted 1 in 4 in RPMI 1640 (Gibco, UK) and centrifuged at 400g for 35 min over a Ficoll-paque gradient (Amersham-Pharmacia Biotech, UK). Cells at the interface were removed and washed once followed by a low speed spin (250g) to remove platelets. Cells were then resuspended in DMEM containing 10% FCS, penicillin 100 units ml⁻¹, streptomycin 50µg ml⁻¹ and glutamine 2mM (Gibco, UK).

15 **Inhibitor dilutions**

Inhibitor stocks (20mM) were kept as a frozen solution (-20°C) in DMSO. Serial dilutions of inhibitors were performed in DMSO as 250-times concentrated stocks. Inhibitors were diluted 1 in 250 into tissue culture media, prewarmed to 37°C and transferred to plates containing PBMC. PBMC and inhibitors were incubated together for 30 mins prior to addition of LPS. Inhibitors used in whole blood assays were prepared according to a different regime. Using the same stock solution serial dilutions of inhibitors were performed in DMSO. Inhibitors were then diluted 1 in 500 straight into whole blood in a volume of 1µL. Inhibitor was incubated with whole blood for 30 mins prior to the addition of LPS.

LPS stimulation of PBMC

PBMC were resuspended at a density of 2x10⁵ cells/well in flat bottomed 96 well tissue culture treated plates. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E coli* strain B5:055, Sigma, at a final

concentration of $1\mu\text{g ml}^{-1}$) and incubated at 37°C in $5\%\text{CO}_2/95\%$ air for 18 hours. $\text{TNF-}\alpha$ levels were measured from cell free supernatants by sandwich ELISA (BioSource #CHC1751).

5 **LPS stimulation of whole blood**

Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), and $500\mu\text{l}$ of blood aliquoted into each well of a 24 well tissue culture treated plate. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E coli* strain B5:055, Sigma, at a final
10 concentration of $1\mu\text{g ml}^{-1}$) and incubated at 37°C without CO_2 for 18 hours. $\text{TNF-}\alpha$ levels were measured from cell free supernatants by sandwich ELISA (BioSource #CHC1751).

Rat LPS induced TNF release

15 Male Lewis rats (180-200g) are anaesthetised with Isoflur and injected i.v. with LPS* in a volume of 0.5ml sterile saline. After 90minutes blood is collected into EDTA tubes for preparation of plasma samples. Plasma is stored at -70°C prior to assay for $\text{TNF}\alpha$ by commercial ELISA.

20 **Rat CIA**

Female Lewis rats (180-200g) are anaesthetised with Isoflur and immunised i.d. at the base of the tail with $2 \times 100\mu\text{l}$ of emulsion containing 4mg/ml bovine collagen II in 0.01M acetic acid and Freund's Incomplete Adjuvant at a ratio of 1:1. A polyarthritis develops with onset from about 13 days post
25 sensitisation. The disease is mainly confined to the ankles and is quantified by plethysmometry. Results are expressed as change in paw volume over time.

In the p38 inhibitor assays described above compounds of the invention have IC_{50} values of around $1\mu M$ and below. The compounds of the invention are clearly potent inhibitors of p38 kinase, especially p38 α kinase.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☒ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.